

Assessing Exposure to Disinfection By-products in Women of Reproductive Age Living in Corpus Christi, Texas, and Cobb County, Georgia: Descriptive Results and Methods

Michele Lynberg,¹ J.R. Nuckols,² Peter Langlois,³ David Ashley,¹ Philip Singer,⁴ Pauline Mendola,⁵ Charles Wilkes,⁶ Heidi Krapfl,² Eileen Miles,¹ Vanessa Speight,⁴ Bruce Lin,¹ Leanne Small,² Amy Miles,⁴ Michael Bonin,¹ Perri Zeitz,¹ Altaf Tadkod,¹ Judy Henry,³ and Mathias B. Forrester³

¹Centers for Disease Control and Prevention's National Center for Environmental Health—Division of Environmental Hazards and Health Effects, and Division of Environmental Health Laboratory, Atlanta, Georgia, USA; ²Department of Environmental Health Colorado State University, Fort Collins, Colorado, USA; ³Texas Department of Health, Austin, Texas, USA; ⁴University of North Carolina Department of Environmental Sciences and Engineering, Chapel Hill, North Carolina, USA; ⁵U.S. Environmental Protection Agency National Health and Environmental Effects Research Laboratory, Chapel Hill, North Carolina, USA; ⁶Wilkes Technologies, Inc., Bethesda, Maryland, USA

We conducted a field study in Corpus Christi, Texas, and Cobb County, Georgia, to evaluate exposure measures for disinfection by-products, with special emphasis on trihalomethanes (THMs). Participants were mothers living in either geographic area who had given birth to healthy infants from June 1998 through May 1999. We assessed exposure by sampling blood and water and obtaining information about water use habits and tap water characteristics. Two 10-mL whole blood samples were collected from each participant before and immediately after her shower. Levels of individual THM species (chloroform, bromodichloromethane, dibromochloromethane, and bromoform) were measured in whole blood [parts per trillion (ppt)] and in water samples (parts per billion). In the Corpus Christi water samples, brominated compounds accounted for 71% of the total THM concentration by weight; in Cobb County, chloroform accounted for 88%. Significant differences in blood THM levels were observed between study locations. For example, the median baseline blood level of bromoform was 0.3 ppt and 3.5 ppt for participants in Cobb County and Corpus Christi, respectively ($p = 0.0001$). Differences were most striking in blood obtained after showering. For bromoform, the median blood levels were 0.5 ppt and 17 ppt for participants in Cobb County and Corpus Christi, respectively ($p = 0.0001$). These results suggest that blood levels of THM species vary substantially across populations, depending on both water quality characteristics and water use activities. Such variation has important implications for epidemiologic studies of the potential health effects of disinfection by-products. **Key words:** biomarkers, disinfection by-products, epidemiology, exposure assessment, exposure modeling, tap water, trihalomethanes. *Environ Health Perspect* 109:597–604 (2001). [Online 8 June 2001]

<http://ehpnet1.niehs.nih.gov/docs/2001/109p597-604lynberg/abstract.html>

Recent epidemiologic studies of disinfection by-products (DBPs) have suggested an association between DBPs in tap water and adverse reproductive outcomes, including spontaneous abortion, birth defects, and intrauterine growth retardation (1–5). These studies have reported risks that are relatively consistent but modest in magnitude, with relative risk estimates of 1.5–3.5 among populations exposed to increased levels of DBPs in tap water. Small numbers of cases and limited exposure information complicate interpretation of these results (6,7). Because exposure to DBPs in public water supplies is ubiquitous, even low-magnitude risks (if confirmed) are of potentially great public health importance.

In 1998, the Centers for Disease Control and Prevention's (CDC's) National Center for Environmental Health (Atlanta, GA) and the U.S. Environmental Protection Agency (EPA)—National Health and Environmental Effects Research Laboratory (Research Triangle Park, NC) entered into an Interagency Agreement to conduct a DBP

and birth defects study as part of the existing National Birth Defects Prevention Study (NBDPS). The NBDPS, which began in 1996, is an ongoing case-control study being conducted at eight Centers for Birth Defects Research and Prevention located in Georgia, Arkansas, California, Iowa, New Jersey, New York, Massachusetts, and Texas. Each year, approximately 3,200 infants are enrolled (300 case infants and 100 control infants from each site). Because of significant variation in exposure across these geographic regions and the substantial statistical power afforded by the large sample size, the NBDPS provides an unprecedented opportunity to evaluate the potential association between DBPs and birth defects.

As part of the CDC/EPA collaboration, we are conducting studies to determine the most efficient and accurate exposure metric that can be used in a study of this magnitude. In 1999, we conducted a field study to develop and evaluate, for use in the NBDPS, exposure measures for DBPs with a special emphasis on individual trihalomethanes

(chloroform, bromodichloromethane, dibromochloromethane, and bromoform). This research was integrated with a study by the American Water Works Association Research Foundation (AWWARF) (8). The primary purpose of the AWWARF study was to develop and assess the applicability of predictive equations for the formation of trihalomethanes (THMs) and haloacetic acids (HAAs) in water distribution systems, and to develop tools for linking these equations with epidemiologic studies.

Although most studies of human reproductive outcome and exposure to THMs have focused on total THMs, a recent epidemiologic study (4) that evaluated exposure to individual THM species found an increased risk of spontaneous abortion associated with exposure to bromodichloromethane levels in drinking water above 18 ppb [odds ratio (OR) 3.0, 95% confidence interval (CI) 1.5, 5.9]. Animal data also support the need to evaluate individual THMs. Both chlorinated and brominated THM species (including chloroform, bromodichloromethane, and bromoform) cause reproductive and developmental toxicity in laboratory animals (9–11). Studies of glutathione *S*-transferase-mediated

Address correspondence to M.C. Lynberg, CDC/NCEH/EHHE/HSB, 1600 Clifton Road NE, MS E-23, Atlanta, GA 30333 USA. Express Mail address: 6 Executive Park Drive, Room 1031, Atlanta, GA 30329 USA. Telephone: (404) 639-2587. Fax: (404) 639-2565. E-mail: mcl2@cdc.gov

We appreciate the support and assistance of those individuals who made this study possible: the staff at the Cobb County Marietta Water Authority and the City of Corpus Christi Water Department. In addition, we thank S. Kieszak for her statistical support.

This study was funded in part by the American Water Works Association Research Foundation (AWWARF) and the Texas Birth Defects Research Center (TBDRC) at the Texas Department of Health. AWWARF is funded primarily through annual subscription payments from over 1,000 utilities, consulting firms, and manufacturers in North America and abroad. The TBDRC is funded by the Centers for Disease Control and Prevention, Centers for Birth Defects Research and Prevention Cooperative Agreement #U50/CCU613232.

Received 24 June 2000; accepted 18 December 2000.

mutagenicity suggest that different THM species can induce adverse effects by different mechanisms (12). Brominated THMs cause DNA strand breaks in mice and rats (13). In addition, bromodichloromethane may inhibit some metabolic pathways; genetic variation in specific enzymatic activities may differentially metabolize bromodichloromethane into a highly reactive species (14). Exposure of pregnant mice and rats through inhalation to 100 ppm chloroform caused malformations of their pups; embryo lethality was observed in pregnant rats given doses of 300 ppm (14,15).

Our purpose here is to report the methods and results of our field study and to discuss the potential utility of these specific exposure measures in a large-scale epidemiologic study of DBPs such as the NBDPS.

Methods

Selection of Study Sites

Our study was conducted in Corpus Christi, Texas, and Cobb County, Georgia. We selected these areas because they were within geographic areas represented in the NBDPS and because the water utilities serving them met specified water-quality criteria. These criteria included: *a*) relatively high THM concentrations in comparison to national averages; *b*) high intrasystem differences that would produce a significant gradient in potential exposure across our study population; *c*) one water distribution system with predominantly chlorinated species of THMs and a second water distribution system with predominantly brominated species of THMs; and *d*) a utility service population large enough to allow the rapid ascertainment of 50 mothers willing to participate in our study between July and September 1999.

To select candidate study sites, we used an effective and efficient geographic analysis (16), which combines published information on utility water-quality variation, location, and demographics to screen potential sites for epidemiologic studies of health outcome and tap water. We determined that water supplied by the Cobb County Marietta Water Authority (with predominantly chlorinated DBPs) and water supplied by the City of Corpus Christi Water Department (with predominantly brominated DBPs) met these criteria. We discovered that most large utilities within the NBDPS study region where brominated compounds were likely to occur had switched to chloramination for secondary disinfection (including the City of Corpus Christi Water Department). Chloramination limits further THM formation potential and dampens the spatial variation of THMs in a water distribution system

(17). Thus, for brominated compounds, we anticipated that we could not find a water utility that would meet the second criterion. We decided that low spatial variation of THM concentration in tap water levels in Corpus Christi could provide an opportunity to focus on the effect of personal water use activities and consumption on exposure, assuming differences in THM levels at participants' taps would be statistically insignificant.

Selection of Study Subjects

Using a human subjects-approved study protocol (CDC protocol #2087), we selected subjects from among mothers who had given birth within the previous 18 months and still resided in Corpus Christi, Texas, or the region of Cobb County, Georgia, served by the Wyckoff Water Treatment Facility (one of two water treatment plants that serve Cobb County). We chose the Wyckoff facility with the help of water utility personnel because of its well-defined service area. Mothers were selected from hospital records, and qualified for enrollment if they had borne healthy infants from June 1998 through May 1999. Births that met the selection criteria were oversampled to accommodate an anticipated 50% participation rate. We also obtained contact information from hospital records. Mothers who changed residences but remained within the geographic area served by the utilities being studied were not excluded.

Enrollment continued until each site had 25 mothers willing to participate in all aspects of the study. In Cobb County, 95 letters of invitation were sent to individuals who met the initial enrollment criteria. Mothers who currently resided out of county, did not speak English, or did not have an individual water meter were excluded. Of the 95 potential participants, 69 (73%) appeared to meet the initial selection criteria. Of these, 19 were excluded because they could not be reached by phone (no answer, disconnected, or incorrect telephone number). Half the remaining women (25/50) agreed to participate in the study. In Corpus Christi, 172 letters of invitation were sent to women who met the initial enrollment criteria. Of these, 21 were deemed ineligible, and 87 could not be reached by phone. Forty percent (25/64) of the remainder were included in the study. The length of time between the infant's date of birth and the mother's participation in the study ranged from 4 months to 15 months. According to approved human subjects standards for reimbursement, each study participant was paid \$100.00.

Methods for Assessing Exposure

Methods for assessing exposure to DBPs applied in the study included an initial 10-min telephone interview; a second 30-min telephone interview on water use and consumption; and in-home visits on 2 consecutive days (4–5 hr total). During the in-home visit, a 1.5-day diary concerning water use and consumption patterns was completed by the subject. Besides evaluating exposure through the use of telephone interviews and personal diaries, we assessed several other measures of exposure, including residential water flow; tap water quality; blood THM levels; and residence characterization for use in total exposure modeling to THMs through inhalation, dermal absorption, and ingestion.

Initial telephone interview. At the time of the initial telephone contact, informed consent was obtained and a 10-min telephone interview was conducted. Preliminary questions were asked relating to water consumption and water use to screen participants who would not be eligible (such as residents without individual water meters and residents outside of the study area). For all eligible subjects who agreed to participate, an additional telephone interview and an in-home visit were completed within 15 days, on average, of the first interview (range 2–34 days).

Second telephone interview. In the second telephone interview, we asked participants about the time period from 1 month before conception to the month of the infant's birth. We asked detailed questions about hot and cold water consumption (at home and at work) and water use (e.g., bathing, swimming, household habits). Other questions concerned hand washing, showering and bathing, dish washing (by machine and by hand), clothes washing (by machine and by hand), bathing children, using saunas and hot tubs, and using swimming pools. We also asked about the frequency and duration of these water activities. For each residence in which participants lived during the relevant time period, we asked about water source characteristics (private compared with public supply, chlorination, use of in-home treatment devices).

In-home visits. After the 30-min telephone interview, we conducted in-home visits. On consecutive days, a team of researchers (an environmental engineer, a phlebotomist, and an epidemiologist) visited the participants' homes. Generally, the initial in-home visit took place in the afternoon for about an hour. During this visit, the team answered questions, obtained written informed consent, attached and calibrated a water meter data logger, and conducted a home characterization walk-through. The next day, the team arrived at a prearranged time (usually in the morning) and obtained

two 10-mL blood samples, just before and just after the participant's shower, and duplicate tap water samples.

Because THM levels in blood have a half-life of approximately 0.5 hr (18), we took blood samples as early in the morning as possible (before water use activities were initiated), to provide an estimate of the participant's baseline or steady-state blood levels (assuming no exposure while sleeping). Similarly, because inhalation of THMs while showering is one of the most important and significant routes of exposure (19,20), the samples that were taken as soon after showering as possible were considered an estimate of the peak blood THM level.

While the participant was showering, duplicate water samples were collected from the kitchen sink (or nearest unfiltered tap). Faucets were set to the "coldest" position; samples were collected after letting the water run for 5 min. Water temperatures were not measured at the tap. After the shower and the second blood draw, we introduced and demonstrated the water use diary. The team returned later that evening, retrieved the diary and the water meter data logger, answered questions, and reimbursed study participants.

Water samples. Besides water samples taken at the participant's home, we obtained samples from the water-treatment plants and the distribution systems. Sampling locations in the water distribution systems were strategically selected for use in calibration and validation of a water quality network model (21). During the study period in each study site—July and September 1999 in Corpus Christi; July and August 1999 in Cobb County—we collected approximately 50 water samples from the water distribution system at the point of entry from the water plant to the distribution system, at water storage tanks, and at spatially distributed locations across the pipe network. In addition, we collected a water sample and replicate at each participant's residence during the second day of the in-home visit, near the time of collection of blood samples. We analyzed water samples and replicates for the four individual THMs, free chlorine, and combined chlorine. We analyzed THM concentrations in water samples by liquid-liquid extraction, using capillary column gas chromatography and electron-capture detection according to methods described elsewhere (22). The method has a detection limit of 1 ppb. We also analyzed the water samples for haloacetic acid (HAA) content. All DBP measurements in tap water samples were made at the University of North Carolina Department of Environmental Science and Engineering within two weeks of sample collection.

Whole blood samples. We collected two 10-mL whole blood samples approximately

0.5 hr apart, before and just after the study participant showered. We collected samples by venipuncture into gray top vacutainers (Becton Dickinson Vacutainer Systems, Rutherford, NJ) containing potassium oxalate/sodium fluoride that were specially treated to remove volatile organic compound contamination (23). Whole blood samples were placed on wet ice or stored at refrigerator temperatures. Individual THM species levels (parts per trillion) in whole blood were determined by a modification of the previous heated purge and trap gas chromatography isotope dilution mass spectroscopy procedure (24). The use of selected ion monitoring and a Micromass Ultima mass spectrometer (Micromass, Beverly, MA) lowered detection limits into the parts-per-quadrillion range. All measurements were performed within 8 weeks of collection at the CDC's Environmental Health Laboratory Air Toxicants Branch.

Measurements of residential water flow.

We measured the flow of water within the residence using water meter data loggers (Meter Master Model 100EL; F.S. Brainard Company, Burlington, NJ). These data loggers contain a sensor that is attached to the outside of the water meter. The logger detects and records the change in the magnetic field caused by the rotation of a magnet embedded in the impeller of the meter. As the impeller rotates at a speed proportional to water flow into the residence, the data logger records each revolution. Personal computer-based analysis software (Trace Wizard; Aquacraft Inc., Boulder, CO) separates water use components into individual discrete uses. Events such as toilet flushes, showers, and clothes washing are separated from the total flow signal using signal-processing techniques. If the participant's home had a magnetic water meter, the logger was prepared by recording the logger number, date, time, meter number, meter brand, and meter model. On the first day of the in-home visit, the logger was installed, tested, and calibrated by drawing a known quantity of water run from an outside faucet. The logger was retrieved in the late afternoon/early evening of the following day. Logger data were not available for 10 (20%) of the participants. Although we attempted to exclude participants whose homes did not have magnetic meters or individual water meters (e.g., apartment dwellers), eight participants were subsequently determined at the in-home visit to fall into one of these categories. At two other homes, the logger did not function correctly.

Residence characterization. The environmental engineer on the research team conducted a walk-through evaluation of the participant's residence. During the walk-through, which was similar to a real-estate

appraisal, the engineer sketched the floor plan for each level of the residence, noting the size of each room and location of water-using devices. The engineer conducted water draws of known volume for use in calibration of the water flow meter, turning on each water-using device to provide a "signature" for use in the analysis of information recorded by the data logger. The age, type, and size of each window and exterior door were also noted. The engineer ascertained information concerning air circulation, heating, ventilation, and air conditioning systems used in the home, noting location of supply and return vents. This information was used to estimate transport characteristics within the residence related to the dispersion of volatile compounds (such as THMs) from their source (e.g., shower, washing machine) to other locations in the residence. These data were used in a computer simulation model designed to predict personal exposure to volatile organic compounds (25).

Personal water use and consumption diary. On the second day of the in-home visits, the interviewer introduced the diary to the participant, focusing on the importance of recording all home tap water use and consumption. The previous afternoon/evening was used as an example to demonstrate how the diary works, with the participant and the interviewer completing the diary together. The importance of contemporaneous recall was emphasized, and participants were encouraged to use a variety of strategies to remind themselves to record the event when they used water. This information was used to develop input data for the personal exposure modeling.

Personal exposure modeling. We employed a modified version of the Total Exposure Model (TEM) developed by Wilkes (25) for estimating the uptake of THMs into the bloodstream. TEM predicts the exposure and dose to an individual resulting from use of a contaminated water supply by modeling the fundamental physical and chemical processes that occur during the interaction between the contaminated media (in this case, the air and water) and the exposed individuals. Using finite difference techniques, TEM estimates the mass transfer of the chemicals from the water to the air during water use activities. TEM predicts the resultant water concentrations during use and air concentrations throughout the house. Using these predicted air and water concentrations and location information provided by the field study, TEM estimates potential exposure to the subject. Subsequently, we used uptake models to estimate the mass of contaminant entering the bloodstream. The inhalation uptake model is an equilibrium lung model, described by Wilkes (25). The

dermal uptake model is a skin diffusion model described elsewhere (26). Ingestion uptake is assumed to be 100% absorption of the mass in the water. The dose absorbed through each of the three principal routes of exposure (inhalation, dermal, and ingestion) is estimated using fundamental uptake models. A more complete description of the modeling techniques used by TEM can be found elsewhere (25,27,28).

Required inputs to TEM include housing characteristics, water use and activity of the study participant, water source and

contaminant information, and chemical properties of the contaminant. We used data obtained during the in-home visit to estimate 11 (73%) of the 15 input variables for TEM. The other four input variables (breathing rate, chemical properties, source characterization by water fixture type, and water temperature) were derived from other databases (29–31). To provide information on all aspects of our exposure assessment approach in this paper, we present the results of applying TEM for one compound, chloroform, to one study participant and her residence.

Table 1. Median and Interquartile ranges of THM Levels (ppb) in Cobb County and Corpus Christi homes, water treatment plants, and distribution systems.

Trihalomethane species	Cobb County			Corpus Christi		
	Home (n = 25)	Distribution system (n = 20)	Water treatment plant (n = 7)	Home (n = 25)	Distribution system (n = 30)	Water treatment plant (n = 20)
Chloroform						
Median	84.8	79	49.5	8.2	4.6	6.1
Interquartile range	72.1, 96.7	57.2, 88.5	42.1, 52.1	5.4, 10.8	4.2, 6.5	4.2, 8.0
Bromodichloromethane						
Median	13.5	12.5	9.5	12.2	8.3	9.5
Interquartile range	12.4, 16.0	12, 14.3	8.9, 10.2	8.8, 12.8	6.7, 9.8	8.1, 11.6
Dibromochloromethane						
Median	1.7	2.4	1.4	13.5	12.6	14.3
Interquartile range	1.6, 2.4	1.7, 3.6	0.5, 1.7	11.0, 15.2	10.3, 13.7	12.1, 16.6
Bromoform						
Median	ND	ND	ND	8.7	9.7	11.9
Interquartile range	—	—	—	5.8, 13.1	7.7, 12.5	7.8, 14.7
Total						
Median	100.2	92.8	61	43.7	35.0	41.5
Interquartile range	86.8, 116.7	72.6, 108	53, 65.3	37.5, 46.9	29.8, 43.4	37.1, 49.0

ND, not detectable (limit < 1 ppb).

Table 2. Between-site comparison of median blood levels (before and after shower) and changes in blood levels (Δ).

Species	Before shower		After shower		Δ^a	
	Cobb	Corpus	Cobb	Corpus	Cobb	Corpus
Chloroform						
Median	70	25	280	57	189	25
Interquartile Range	52, 103	17, 42	205, 435	39, 67	133, 373	13, 39
p-Value	0.0001 ^b		0.0001 ^b		0.0001 ^c	
p-Value					0.0001 ^d	
Dichlorobromomethane						
Median	6.2	6.8	38	43	30	34
Interquartile range	5.2, 9	4.6, 10	26, 69	31, 60	18, 61	23, 46
p-Value	0.9362 ^b		0.8103 ^b		0.0001 ^c	
p-Value					0.8650 ^d	
Dibromochloromethane						
Median	1.2	7.0	6.1	41	5.0	35
Interquartile range	0.9, 1.5	4.2, 10	4.3, 11	32, 53	3.3, 9.4	21, 48
p-Value	0.0001 ^b		0.0001 ^b		0.0001 ^c	
p-Value					0.0001 ^d	
Bromoform						
Median	0.3	3.5	0.5	17	0.2	12
Interquartile range	0.1, 0.4	2.0, 5.6	0.3, 0.8	10, 23	0.1, 0.3	8.6, 20
p-Value	0.0001 ^b		0.0001 ^b		0.0003 ^c	
p-Value					0.0001 ^d	
Total THM						
Median	80	52	318	171	223	119
Interquartile range	57, 112	33, 84	241, 516	126, 212	157, 443	77, 157
p-Value	0.0257 ^b		0.0001 ^b		0.0001 ^c	
p-Value					0.0001 ^d	

^aIncrease in blood THM level (difference between after showering and before showering blood levels). ^bComparison of medians between Cobb County and Corpus Christi. ^cComparison of median Δ with zero. ^dComparison of median Δ between Cobb County and Corpus Christi.

Statistical methods. We entered all data into a Microsoft ACCESS database (Microsoft, Redmond, WA) and completed statistical analyses for comparisons of blood and water THM levels using SAS Version 6.2 (SAS Institute, Cary, NC). We made comparisons within and between study sites for individual and total THMs in blood and water. We compared the following blood levels for individual THMs: *a*) changes in blood levels (Δ) after shower; *b*) between-site differences in blood levels before shower; *c*) between-site differences in blood levels after shower; and *d*) between-site comparison of blood level changes. We used nonparametric statistics because not all data were normally distributed, the sample size was small, and some data were out of range (either below the detection limit or above the highest linear standard). We used Wilcoxon signed rank tests to compare the paired blood THM levels for each individual (before and after shower). We used Wilcoxon rank sum tests to evaluate the differences in median blood THM levels between sites. We compared median THM levels in water samples from participants' homes, utility distribution systems, and treatment plants using Wilcoxon rank sum and Kruskal-Wallis tests. We compared reported water use activities and drinking water consumption frequencies using Fisher's exact test.

Results

THM levels in the water distribution system and in tap water of study participants. We made inter- and intrasystem comparisons for THM levels in water samples from Corpus Christi and Cobb County (Table 1). Except for bromodichloromethane levels at the water treatment plants, all intersystem differences were statistically significant ($p = 0.0001$). For example, the median level of chloroform in water samples taken from homes in Cobb County was significantly higher than in Corpus Christi, as were levels in samples from the distribution systems and the treatment plants. The brominated species were significantly lower in Cobb County than in Corpus Christi ($p = 0.0001$), with almost no bromoform or dibromochloromethane in Cobb County. In the tap water samples for Corpus Christi, brominated compounds accounted for 71% of the total THM concentration by weight, whereas in Cobb County they accounted for less than 16% (chloroform accounted for 84%). Median total THM levels at the plant, in the distribution system, and in the homes of participants were appreciably higher in Cobb County than in Corpus Christi.

As expected, speciation and concentration of THMs in the tap water samples from the homes of study participants reflected

those found in the water samples from each utility's distribution system. Also as expected, variation of THM levels across all water samples within the chloraminated Corpus Christi system was lower than in Cobb County, which uses free chlorine. However, both systems had significant differences in THM levels among water samples taken at home, in the distribution system, and the treatment plant (Table 1). In Corpus Christi, the median total THM levels at the plant, distribution system, and residences were 41.5 ppb, 35.0 ppb, and

43.7 ppb, respectively. The median total THM levels in Cobb County increased from 61 ppb at the plant to 92.8 ppb in the distribution system and 100.2 ppb in the residences of participants.

THM levels in the blood of study participants. We compared pre-shower blood THM levels between Cobb County and Corpus Christi (Table 2). Pre-shower blood levels were significantly different for each of the THM species except bromodichloromethane. After-shower blood levels were also significantly different between the two study sites (p

$= 0.0001$). Statistically significant increases in blood THM levels occurred after the shower for all THMs (individual and total) (Table 2).

The relative change in blood levels (after versus before showering) between sites was also compared. Except for bromodichloromethane, increases in chloroform and total THM blood levels were significantly greater in Cobb County than in Corpus Christi. Increases in bromoform and dibromochloromethane blood levels were significantly greater in Corpus Christi.

Drinking water consumption. We evaluated the drinking water consumption habits of mothers living in Corpus Christi and Cobb County at home and at work. Participants reported drinking between 3 and 21 glasses of cold water (including beverages made with cold water) per day. Mothers who worked outside the home in either Corpus Christi or Cobb County reported drinking more water per day than did mothers who did not work outside the home; however, this difference was not statistically significant (Table 3). Among mothers who worked outside the home, mothers in Corpus Christi reported drinking more glasses of water per day than did mothers in Cobb County ($p = 0.043$). Only 21% of mothers who worked outside the home in Corpus Christi changed the type of water they drank while at work (generally from tap to bottled water), compared to 78% of Cobb County participants (data not shown). There were no other significant differences in the amount of water consumed.

Water use based on the interview. Table 4 summarizes the water use habits of mothers living in Cobb County and Corpus Christi. Except for taking baths and using hot tubs, most mothers reported participating in each of the individual water use activities. In both Cobb County and Corpus Christi, more mothers reported taking showers than reported taking baths. Most participants took showers exclusively; only 6% took baths exclusively. Although the number of participants who showered was similar between the two communities, the reported frequency of showering differed significantly ($p = 0.01$). Participants in Corpus Christi reported more frequent and longer showering than mothers in Cobb County; 64% of participants in Corpus Christi and 32% of participants in Cobb County reported taking showers more than 10 min in length (data not shown). Differences in other water use activities were not statistically significant.

Personal exposure modeling. In this paper, we present the results from an example run of TEM (25) for one participant and her residence in Corpus Christi. Figure 1 is a plot showing time and flow rate of recorded water uses in the residence during the morning of

Table 3. Median number of glasses of water consumed per day at home and at work.

Study site and work outside the home	Total	Home	Work
Corpus Christi ($n = 25$)	9	5	—
Mothers working outside the home ($n = 19$)	10	6	3
Mothers not working outside the home ($n = 6$)	5	5	NA
Cobb County ($n = 25$)	8	5	—
Mothers working outside the home ($n = 18$)	8	5	3
Mothers not working outside the home ($n = 7$)	8	8	NA

NA, not applicable.

Table 4. Percentage of participants in Cobb County and Corpus Christi who reported specific water use habits.

Water use activities	Cobb County $n = 25$	Corpus Christi $n = 25$	Total $n = 50$
Hand washing	100	100	100
2–4 times per day	24	32	28
5–6 times per day	36	40	38
8–10 times per day	16	12	14
≥ 11 times per day	24	16	20
Dish washing by hand	80	100	90
2–5 times per week	24	8	16
7 times per week	28	44	36
8–12 times per week	0	20	10
14 times per week	12	16	14
≥ 16 times per week	16	12	14
Dish washing by machine	96	40	68
1–2 times per week	4	8	6
3 times per week	16	16	16
4–6 times per week	40	8	24
7 times per week	36	8	22
Clothes washing by machine	96	92	94
1–3 loads per week	12	16	14
4 loads per week	28	20	24
5–7 loads per week	32	28	30
≥ 8 loads per week	24	28	26
Showering	92	96	94
1–6 times per week	16	4	10
7 times per week	48	28	38
8–13 times per week	28	36	32
14 times per week	0	28	14
Taking baths	40	36	38
1 time per week	16	16	16
2–3 times per week	8	16	12
6–7 times per week	16	0	8
Bathing children	56	68	62
1–3 times per week	16	4	10
4–6 times per week	16	8	12
7 times per week	16	28	22
8–10 times per week	4	16	10
14–15 times per week	4	12	8
Hot tub use	8	20	14
Swimming pool use	56	60	58
1 time per month	4	12	8
2 times per month	20	16	18
3–4 times per month	12	20	16
≥ 5 times per month	16	12	14

day 2 of the in-home visit. During the 24-hr modeling period (5:00 P.M. on day 1 until 5:00 P.M. on day 2), 46 water uses were separately recorded and validated for the residence used in this example. By analyzing the data logger information coupled with the personal diary information, we identified and characterized use of specific water appliances in the residence by the study participant. We have labeled examples of these water uses in Figure 1 to demonstrate this capability. Location, duration, and volume associated with each use can be derived from this information. For example, in Figure 1, the shower by the participant at 9:22 A.M. on day 2 lasted 3.5 min and used a volume of 8.2 gal.

The plot in Figure 2 demonstrates how the water use information plotted in Figure 1 can be used in conjunction with TEM (25) to estimate potential exposure. In this example, we show the plot of two output variables from the inhalation component of TEM for chloroform. The variables are personal environment concentration (PEC) and cumulative absorbed dose (CAD). PEC is the predicted concentration in the breathing zone of the subject, which is based on her location in the residence and on the predicted concentration of chloroform in the air at that location. The air concentration of chloroform is predicted by the model based on timing, location, and use of water by specific appliances; air circulation within the home; and concentration of the target compound in the tap water (25). CAD is the mass of the contaminant (milligrams) that is predicted by the model to be absorbed into the bloodstream in the lungs during the modeling period.

The inset table in Figure 2 summarizes the predicted CAD for chloroform for each route of exposure over the 24-hr modeling period. For this study participant, inhalation accounted for approximately 98% of the calculated 24-hr chloroform dose.

Discussion

Using sophisticated analytic techniques, we were able to quantify blood levels of volatile compounds at extremely low concentrations

(parts per trillion), enabling us to discern elevated blood THM levels among study participants. This is the first study that we are aware of that documents elevated background levels of individual THMs in human tissue; demonstrates substantial differences in speciation and blood levels of THMs between populations served by different water supply systems; and indicates THM speciation and levels in blood mirror the THM speciation and levels found in an individual's water supply.

We found that median blood levels of chloroform, dibromochloromethane, and bromoform in participants in Cobb County differ significantly from those of participants in Corpus Christi. These differences were apparent even in early morning (pre-shower) samples when exposure from tap water use and consumption should have been at a minimum. The statistically significant differences we observed in blood THM level and speciation were concordant with the statistically significant differences in THM level and speciation in the water supplies of the two study populations. For each THM species, the concentration found in the blood samples was about 1/1,000 the level found in the resident's tap water (data not shown). This is consistent with the general observation that biologic levels of unmetabolized compounds in humans are orders of magnitude lower than levels found in the environment. A similar relationship between level of exposure and concentration of HAAs in blood and milk has been found in studies of rabbits (32). Although the biologic significance of blood THM levels is unknown, the ability to measure these differences clearly provides an important tool for epidemiologic studies of DBPs and adverse health outcomes.

We also found significant differences between pre-shower and postshower blood THM levels. Because the half-life of volatile compounds in the blood typically is about one-half hour or less (33,34), blood THM levels are strongly influenced by exposures

occurring minutes to hours before the sampling. While this may suggest that exposure to this class of compounds is a transient event, the short half-life is misleading. Controlled pharmacokinetic experiments have shown that the uptake and excretion of volatile compounds are complex processes (18). A small but measurable fraction of the absorbed dose is deposited in longer-lived sites (18,33,35). Although the degree to which bioaccumulation occurs is unknown, exposures occurring several days before sampling are also influential, particularly recurring exposures (33). Assuming that our pre-shower blood samples represent a background level and that the differences we observed in these blood levels are caused by repeated and relatively consistent exposure to THMs in an individual's water supply, the elevated pre-shower blood levels of bromoform and dibromochloromethane in Corpus Christi participants further support the findings of other studies that rapidly excreted chemicals can accumulate in body tissues and fluids (18,33,35).

Besides the variation in blood THM levels, we found significant spatial (intrasystem) variation in levels of THMs at locations across each of the water distribution systems. Spatial variability in the level of DBPs in the water supply of study participants can significantly affect exposure estimates and conclusions of epidemiologic studies (3,4,6,16). For example, Gallagher et al. (3) excluded almost one-half of their original study population because they could not account for intrasystem variability in THM levels. Likewise, Waller et al. (4) are reevaluating the exposure metric used in their study concerning DBPs and spontaneous abortion partly because of this same issue (36). Our findings strongly suggest that the degree of intrasystem variation in water supply DBP levels is a very important factor in the design of an epidemiologic study. Researchers should be cautious in using average values from utility monitoring data as a surrogate for exposure; the degree of intrasystem variation and resultant exposure misclassification that can be tolerated in such epidemiologic studies is uncertain.

The finding of spatial variance in THM levels in the Cobb County system replicates findings of other researchers studying the distribution of THM levels in water systems using free chlorine for disinfection (3,37–41). However, these findings were not expected in Corpus Christi, which uses chloramination for disinfection; after water treatment, chloramination attenuates the further production of THMs in the distribution system (17). It is most likely that the spatial variation observed in THM levels across the Corpus Christi study area is caused by important

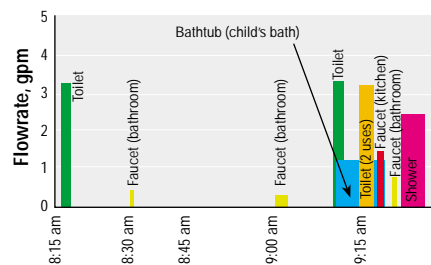


Figure 1. Use information derived from water meter data logger for a study residence in Corpus Christi, Texas.

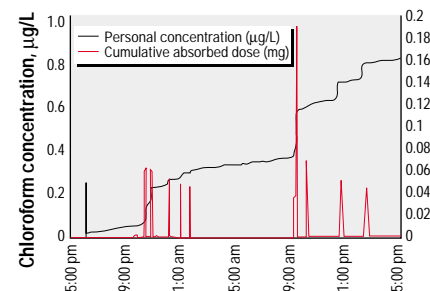


Figure 2. Results of application of Total Exposure Model (25) for chloroform to a study residence and participant in Corpus Christi, Texas. Dose summary: inhalation, 0.161 mg; dermal, 0.004 mg; ingestion, 0 (consumed bottled water).

determinants of THM levels in a water distribution system (including water distribution and storage system hydraulics, temporal variation in water produced by the water treatment plant, and timing of sample collection) (16, 38–41). Nonetheless, the fact that statistically significant intrasystem variation in THM levels can exist in a chloraminated water distribution system is an important finding; insignificant intrasystem variation should not be assumed in epidemiologic studies of populations residing in chloraminated systems.

From an exposure assessment perspective, the high degree of variation in blood THM levels among individuals living within each of our study areas is an important consideration. For example, the pre-shower chloroform levels of study participants in Cobb County ranged from 130 ppb to 1,100 ppb (over an 8-fold difference). Using a separate analysis of data from our field study, Miles et al. (42) found that tap water concentrations explained a statistically significant portion of the variation in THM concentrations measured in the blood. However, this relationship was not a simple linear one, indicating that other factors, such as water use activity patterns, may be important in determining THM concentrations in the blood.

In addition, the time window of exposure represented by the pre-shower background blood levels in our study remains unclear. We collected blood and water samples concurrently. Thus, each sampling event represents a “snapshot” measure of blood and water THM levels. However, the findings of our study clearly indicate an association between blood and water THM levels.

We demonstrate that differences in individual water use activities can significantly influence the level of THMs reaching the blood stream. We report on the feasibility of using a computer model (25) in conjunction with a water use data logger to predict mass transfer of THMs from an individual's environment to his or her blood supply with consideration given to the route of exposure. Preliminary results from the application of this technology support the theory that other water use activities in the home besides showering contribute to the variation in blood THM levels in our study population. These findings are consistent with evidence from studies that suggest routes of exposure other than ingestion are important to consider in assessing exposure to DBPs (43–48).

Limitations of our study included a small sample size and only two study locations. With such an intense data collection effort for each subject, however, it was not feasible to study larger numbers of subjects over several locations. Because only two locations were selected (with high contrasts in the

concentration of specific THMs), it is difficult to generalize comparisons across study locations and distribution systems. Another limitation is our low participation rates (44%), which resulted mainly from insufficient time to spend in persistent tracing of all eligible subjects. Thus, our study subjects may not be truly representative of the populations residing in Corpus Christi or Cobb County; it could be imprudent to extrapolate the prevalence of exposures (e.g., number of glasses of water consumed per day) to the general population of mothers with young children. However, because the main objective of this field study was to describe the relationship between different measures of exposure within individuals and between populations served by water systems with highly contrasting concentrations and speciation of THM compounds, we contend that the impact of selection bias on these relationships is likely to be within acceptable limits.

This study's substantial strength was an interdisciplinary approach based on collaboration between scientists with diverse backgrounds, including epidemiology, engineering, and environmental health sciences. This study provided a unique opportunity to evaluate DBP exposure measures and, in turn, define practical and useful measures of exposure in future studies of DBPs and adverse health outcome. Using sophisticated analytic techniques, we were able to quantify blood THM levels at extremely low concentrations, evaluate DBP exposure measures derived from intensive field data collection, and evaluate the feasibility of using advanced computer-based technology to predict mass transfer of THMs from an individual's environment to his or her blood supply.

Our study demonstrates that further efforts are needed to develop improved exposure assessment methods for epidemiologic studies of exposure to tap water, especially studies concerning DBPs.

We have identified several important areas of research, including the determination of which individual exposure measures are most important in assigning an exposure classification and the development of methods for obtaining information that will produce appropriate and accurate estimates of these variables.

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